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Paroxysmal nocturnal hemoglobinuria: patient journey and burden of disease

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SUMMARY

Patients with paroxysmal nocturnal hemoglobinuria (PNH) often experience a lengthy path to diagnosis. Fewer than 40% of patients with PNH receive a diagnosis within 12 months of symptom onset, and 24% of all PNH diagnoses can take 5 years or longer. Diagnostic delay is a source of distress and can affect emotional well-being for patients with PNH. In PNH disease management, patients and care providers focus on risk of organ failure and mortality related to disease progression; nonetheless, patients' health-related quality of life (HRQOL) is largely affected by extensive treatment requirements and nonfatal complications of disease, such as fatigue. In particular, thrombosis is associated with significant impairments in physical and social functioning and global health status and significant fatigue. Among patients with anemia who are transfusion dependent, the burden of transfusion is considerable. Transfusion dependence has a negative effect on HRQOL; is associated with risks and complications, including iron overload; and results in lost productivity due to travel times to and time spent at infusion centers.

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The Patient Journey

PATH TO DIAGNOSIS

Paroxysmal nocturnal hemoglobinuria (PNH) is multisystemic with nonspecific symptoms and clinical manifestations due to intravascular hemolysis, thrombosis, and bone marrow failure.[1] As a result of the multifactorial symptoms of PNH, many patients experience a lengthy and complex path to diagnosis.[2] According to an online survey of 163 patients with PNH, on average, it takes close to 2 years and often multiple providers to correctly diagnose PNH.[3,4] Fewer than 40% of patients with PNH receive their diagnosis within 12 months of symptom onset, and 24% of all PNH diagnoses can take 5 years or longer.[4] Moreover, 79% of patients consult more than 1 physician before receiving a diagnosis, and of these patients, approximately 38% see 5 or more different physicians across different specialties, such as primary care physicians, hematologists, obstetrician-gynecologists, urologists, mental health specialists, pulmonologists, and neurologists.[4]

The length of time to diagnosis can be a source of distress and affect the patient's emotional well-being, in addition to carrying clinical implications. Patients with PNH are at risk for complications of the disease before diagnosis: It is estimated that 40% of patients have experienced a thromboembolic event before diagnosis.[5] In addition, the length to and the uncertainties surrounding a diagnosis can be psychologically distressing for patients and their families.[3] The survey of 163 patients with PNH found that some patients described their journey to a diagnosis as "periods of hopelessness and anxiety" that had a long-lasting effect on their lives.[3] Because PNH can present with changing symptoms, care episodes appeared disconnected for many patients, and some felt isolated, anxious, and dismissed by medical personnel.[3] Despite the potential severity, most patients felt relief once the diagnosis of PNH was reached; subsequently, patients felt fear, since few were aware of this type of disease. Although 54% of patients consulted a primary care physician, approximately 15% went to the emergency department to receive care. A minority of patients saw hematologists or obstetrician-gynecologists for an initial evaluation (11% and 7%, respectively). Only one third of these patients seeking help for their symptoms were later referred to a hematologist.[3]

Patients who present with a Coombs-negative hemolytic anemia, aplastic anemia, refractory anemia, and unexplained thrombosis, especially in atypical locations (cerebral, dermal, and intra-abdominal vein thrombosis, and Budd-Chiari syndrome) co-occurring with cytopenia or hemolysis, are generally screened for PNH.[6] If PNH is suspected, the physician may order different blood tests.[6] Flow cytometric evaluation of the peripheral blood to assess for glycosylphosphatidylinositol (GPI)-anchored protein in at least 2 lineages (i.e., red and white blood cells) is the gold standard for diagnosis, as it is the most sensitive and reliable diagnostic test that confirms the presence of a PNH clone.[7] Flow cytometry allows not only the detection of GPI-deficient cells but also the ability to quantify the proportion of the mutant cells and the specific population of blood cells most affected by the mutation.

Burden of Disease

HEALTH-RELATED QUALITY-OF-LIFE BURDEN

In PNH disease management, physicians largely focus on the risks of organ failure and mortality related to disease progression. Although these areas are of interest in the treatment of the disease, patients' health-related quality of life (HRQOL) is largely affected by nonfatal manifestations of disease progression, such as fatigue, and extensive treatment requirements.[8] These complications limit a patient's ability to complete normal daily activities.[9] There is currently a lack of literature using disease-specific measurement tools to adequately document the patient experience in PNH. Studies have relied on measures such as the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) and the Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-Fatigue), which are used in evaluations of HRQOL among patients with cancer, to collect data from the PNH population.[9,10]

However, development efforts for PNH-specific patient-reported outcome (PRO) measures are underway. The PNH Symptom Questionnaire (PNH-SQ), which was developed in accordance with U.S. Food and Drug Administration guidance for PRO measures, has demonstrated content validity in patients with PNH and will undergo psychometric evaluation using clinical trial data.[11] In addition, an aplastic anemia/PNH-specific quality-of-life instrument has been developed, iteratively refined, and is currently undergoing psychometric evaluation, with plans to include the tool in the assortment of questionnaires used with the International PNH Registry.[10,12]

International PNH Registry. The International PNH Registry was initiated to evaluate disease burden, progression, and clinical outcomes for patients with PNH.[13,14] As of July 2017, the registry had enrolled 4,439 patients worldwide.[14] An analysis of data from the registry was conducted to evaluate the participants' HRQOL using the FACIT-Fatigue and EORTC QLQ-C30, version 3.0.[14] FACIT-Fatigue scores (among 1,894 patients with available data) indicated a clinically meaningful level of fatigue (median [Q1, Q3] scores of

34.0 [27.0, 40.0]). FACIT-Fatigue scores range from 0 to 52, with higher scores indicating less fatigue. EORTC QLQ-C30 Global Health Status (GHS)/Quality of Life (QOL) scores (among 1,888 patients with available data) indicated impaired HRQOL (median [Q1, Q3] scores of 58.3 [41.7, 75.0]). EORTC QLQ-C30 scores range from 0 to 100, with higher scores indicating better HRQOL. Patients enrolled in the registry experienced considerable disease-related fatigue and impairment in overall HRQOL relative to normative reference mean (SD) scores for the general adult population (FACIT-Fatigue: 43.6 [9.4]; EORTC QLQ-C30 Global Health/QOL: 75.5 [19.8]).[14,15]

For patients with PNH, thrombosis in particular is associated with significant impairments in physical and social functioning and global health status and significantly greater fatigue.[13] In an analysis of the first 1,610 patients enrolled in the registry worldwide, patient-reported EORTC QLQ-C30 and FACIT-Fatigue assessments indicated that, when compared with patients without a history of thrombosis, patients with a past thrombosis event had significantly lower GHS/QOL, physical functioning, and social functioning and significantly worse fatigue. In addition, patients reporting abdominal pain, chest pain, confusion, dysphagia, dyspnea, erectile dysfunction, fatigue, headache, hemoglobinuria, or scleral icterus in the 6 months before the study had statistically significantly worse HRQOL scores for all EORTC domains compared with patients who had not experienced each of those symptoms.[13] Mean EORTC QLQ-C30 scores for the GHS of 63.7 and 57.5 in patients with PNH without and with a history of thrombosis, respectively, indicate that PNH has a clinically meaningful effect on HRQOL in all patients (at a 5-point threshold, relative to a reference score of 71.2 for the general population).[13] In addition, mean FACIT-Fatigue scores of 35.9 and 33.4 in patients without and with a history of thrombosis, respectively, indicate a clinically meaningful greater level of fatigue (at a 3-point threshold, relative to reference scores of 43.6 in the general population and 40.0 in patients with cancer without anemia).[13]

Surveillance Registry in Japan. As part of postmarketing surveillance, 491 patients with PNH who were treated with eculizumab after approval were registered in a postmarketing surveillance data registry in Japan as of March 2017. Among the patients enrolled between June 2010 and March 15, 2017, patients with available QOL data at baseline and at 1 year after eculizumab treatment were chosen for analysis (n=54). Quality of life was assessed using the FACIT-Fatigue version 4 in Japanese and EORTC QLQ-C30 version 3 in Japanese.[16]

Overall, results showed that, after administration of eculizumab over 1 year, most QOL domains improved in comparison with baseline. In particular, significant improvement of EORTC QLQ-C30 scores was observed in fatigue, dyspnea, physical function, and GHS. Decreases in lactic dehydrogenase (LDH) and increases in hemoglobin showed strong correlations with QOL improvement. QOL improvement was independent of patients' baseline characteristics of co-occurrence of bone marrow failure or the degree of LDH level.[16]

FACIT-Fatigue and EORTC QLQ-C30 GHS and functioning scores indicated clinical and statistical improvements after 1 year of eculizumab treatment.[16] For EORTC QLQ-C30 symptom scales, most showed clinical and statistical improvement at 1 year, particularly fatigue (mean [SD] scores of 61.2 [32.5] at baseline and 34.7 [25.3] at 1 year; $P<0.01$) and dyspnea (61.6 [37.2] vs. 37.1 [34.4], respectively; $P<0.01$).[16] Despite improvements with treatment, however, patients in this study treated with eculizumab for 1 year experienced continued disease-related fatigue and impairment in overall QOL relative to normative reference scores for the general adult population.[14–17]

Genetic variants in C5 do exist, and poor response to treatment has been reported among Japanese patients with PNH who received eculizumab.[18] The prevalence of this mutation among the patients with PNH (3.2%) was similar to that among healthy Japanese persons (3.5%). This polymorphism was also identified in a Han Chinese population. A patient in Argentina of Asian ancestry who had a poor response had a very similar mutation.[18]

BURDEN OF CHRONIC ANEMIA, FATIGUE, AND TRANSFUSION

Chronic anemia, fatigue, and the need for transfusion are common outcomes for patients with PNH. While evidence of the clinical and HRQOL burden in patients with PNH is limited, evidence from other disease areas, including oncology, suggests that the burden of chronic anemia, fatigue, and the need for transfusion are considerable.

Chronic Anemia. Anemia is a symptom of an underlying disease of various etiologies. Generally, anemia develops when there is an imbalance between production and/or release of red blood cells (RBCs) by the bone marrow and the loss of RBCs in the circulation.[19] The imbalance caused on either side can stem from multiple causes, such as malnutrition or bone marrow failure leading to decreased production or release of RBCs and inherited or acquired hemolytic anemia leading to increased loss of RBCs.[19]

Chronic anemia is detrimental to organ function, as it results in a decreased oxygen-carrying capacity of the blood. During the short term, the body is able to counteract

with an increase in heart rate and respiratory rate; left untreated, severe anemia can cause multi-organ failure. This can include high output heart failure, enlarged heart, myocardial infarction, angina, arrhythmias, cognitive impairment, and renal failure, among other conditions.[19-21] In pregnant women, untreated anemia can cause premature birth and low birth weight and has been shown to be a costly complication that exacerbates ongoing hemolysis in PNH.[19,22,23]

In patients with myelodysplastic syndrome (MDS), which is another bone marrow disorder that can be associated with PNH, anemia is a major cause of morbidity, and patients with MDS who have anemia have increased mortality rates.[24] Mortality is mainly mediated through increased occurrences of cardiovascular disease (CVD).[24] Specifically, anemia in patients with MDS may lead to cardiac remodeling, cardiac enlargement, and left ventricular hypertrophy and may intensify ischemia and angina. In fact, up to half of all mortality in patients with MDS is related to CVD.

Fatigue. Anemia and low hemoglobin concentrations have been strongly associated with fatigue in patients with cancer.[25] Fatigue significantly affects overall well-being and interferes with daily activity and work productivity.[25] An analysis of data obtained from 5 randomized clinical trials demonstrated a significant and positive relationship between increasing hemoglobin level and reductions in fatigue. In particular, patients with a hemoglobin improvement of ≥2 g/dL reported significantly greater increases in FACIT-Fatigue subscale scores than patients who did not have the same hemoglobin response.[25] This translated into moderate improvements in physical, emotional, and functional well-being; large improvements in energy and activity levels; perceived overall health; and reduced need for assistance and, therefore, reduced burden for caregivers.[25,26]

An international, prospective, cohort observational study of high-risk (progression to acute myeloid leukemia) patients with MDS revealed that a higher degree of anemia ($P<0.001$) was associated with greater fatigue.[27] Patients who reported a higher level of fatigue had an overall greater symptom burden, such as moderate to severe appetite loss and dyspnea, than patients who reported a lower level of fatigue. Anemia has many symptoms, including shortness of breath, headache, and chest pain, but patients perceived fatigue as having a greater negative effect on their daily lives than many other cancers or treatment-related complications, such as pain and nausea, with important emotional and mental repercussions, such as lack of self-motivation, sadness, frustration, and mental exhaustion.[28] Fatigue is felt as diminished energy level and slowness that interferes with the patient's normal daily routine. Mentally and psychologically, fatigue is shown to affect typical cognitive function, including concentration and memory.[28] Fatigue can also interfere with willingness to continue and adhere to cancer therapy and thus limit the amount of treatment that a patient tolerates, ultimately affecting disease outcomes.[29,30]

Transfusion. Anemia is often treated with RBC transfusions, and chronic anemia in patients with PNH may result in transfusion dependence.[31] Iron overload is a consequence of chronic transfusions and is associated with an elevated risk of morbidity and mortality in patients with MDS.[22] Chronic transfusion may lead to refractory anemia and development of iron overload because the body cannot effectively excrete excess iron.[32] Iron is, therefore, deposited in parenchymal tissues and in reticuloendothelial cells, and without a chelating therapy, iron overload can cause progressive damage to the liver, heart, endocrine system, brain, and joints.[32,33] Hepatomegaly, liver dysfunction, heart failure, skin pigmentation, hypogonadism, diabetes mellitus, or arthropathy may occur in patients experiencing iron overload.[32] A retrospective evaluation of 13 transfusion-dependent patients (>2 units per month) with acquired chronic refractory or inherited anemia who were reliant on transfusions for more than a year showed that 10 patients had abnormal liver function and 4 patients were diagnosed with heart failure.[32] Serum ferritin levels increased from 1,830 to 5,740 ng/mL in all patients, and skin pigmentation, liver dysfunction, and endocrine dysfunction were observed in 9 patients with serum ferritin >3,500 ng/mL, 8 of whom died.

Transfusion-dependent patients may progress to secondary iron overload with organ impairment, which may be fatal in those who are heavily iron overloaded.[32] A study of transfusion-dependent Japanese patients with MDS, aplastic anemia, and other conditions concluded that mortality is higher in heavily iron-overloaded patients, caused primarily by liver and cardiac dysfunction.[33] This study followed 292 patients who received a mean of 61.5 units of RBCs in a year. There were 75 deaths, of which 24% and 6.7% from these studies were reported as cardiac and liver failure, respectively, which were attributed to iron overload.[33]

Transfusion dependence has a negative effect on a patient's HRQOL and also requires substantial resources, including hospital admissions.[22] A systematic literature review of the burden associated with chronic RBC transfusions in patients with MDS showed that transfusion-related risks and complications can include allergic or anaphylactic transfusion reactions, infections, development of antibodies to RBCs or other blood components, and skin rashes. Regardless of MDS risk score, patients with MDS who required transfusion had reduced overall survival relative to patients with MDS who did not require transfusions.[22] Although transfusions can increase hemoglobin level acutely, patients can still experience long periods of

suboptimal hemoglobin level, which can cause fatigue in addition to the physiologic effect of iron overload and cardiac events increasing risk of mortality.[22]

Transfusion is also associated with time burden and lost productivity due to travel to infusion centers.[34,35] To assess the burden of transfusion on patients, in terms of time spent, a retrospective chart review at multiple outpatient centers in the United States of patients with cancer receiving transfusion was conducted.[34] The mean elapsed time between pretransfusion and posttransfusion vital sign assessment was 4.2 hours (95% CI = 3.64-4.81), including 3.6 hours (95% CI = 3.0-4.1), on average, for patients to receive the actual RBC transfusion treatment. Patients had also an average one-way travel time of 30.0 minutes (95% CI = 25.9-34.3).[34]

In addition, a pilot study of 120 patient records from a private oncology practice or local institutional transfusion center in the United States found that the average patient visit to an outpatient facility ranged from 3.55 hours for 1 packed red blood cell (PRBC) unit to 6.85 hours for 3 PRBC units; 90% of the patients at the facility received 2 PRBC units.[35] In addition to costs associated with pretransfusion testing, transfusion administration, and transfusion-related complications, a number of U.S. national organizations have ongoing initiatives to reduce the use of transfusions.[36,37] Programs have found reduction of 2 units of blood on a regular basis reduced mortality by 18% and resulted in significant cost savings (e.g., $600,000) to large U.S. health systems.[38]

Taking all factors into account, time burden associated with transfusion may be substantial, which is often in addition to the time burden of chemotherapy treatments considerably affecting the patient's QOL.[34,39]

CAREGIVER BURDEN

Patients with a low hemoglobin level (≤12 g/dL) may not be able to work at all, affecting primary caregivers. Caregivers may experience significant impact on their occupational productivity because of the need to reduce their work hours and days.[28]

ECONOMIC BURDEN

Productivity costs are particularly important for PNH because of the substantial time commitments required from patients and their caregivers for the intravenous administration of treatments (either eculizumab or ravulizumab) at infusion clinics. Levy et al. (2019)[40] compared the lost productivity for patients in the United States with PNH managed with eculizumab (administered every 2 weeks[41]) and ravulizumab (administered every 8 weeks[42]) delivered in an infusion clinic and at home.

A set of assumptions were generated using the literature and expert opinion to establish the total time needed for treatment, including administration, recovery, and travel times for each treatment regimen. The total duration was multiplied by an hourly wage of $20 to estimate lost productivity. Results showed that treating 100 patients with PNH in a clinic for 2 years with eculizumab is estimated to result in a total duration of 25,920 hours in travel, administration, and recovery, yielding $518,400 in lost productivity. The less frequent dosing of ravulizumab resulted in $184,800 lost productivity (reduction of 64%). Relative to clinical settings, home treatment reduced lost productivity by $320,000 (38%) for eculizumab and $154,000 (70%) for ravulizumab.

Conclusions

Fewer than 40% of patients with PNH received their diagnoses within 12 months of symptom onset, and a quarter of all PNH diagnoses can take 5 years or longer. Diagnostic delay can be a source of distress and affect patients' emotional well-being. PNH is characterized by intravascular and extravascular hemolysis, leading to severe anemia and other debilitating symptoms. If untreated, anemia can cause multi-organ failure, including heart failure, angina, arrhythmias, cognitive impairment, and renal failure. RBC transfusion is time consuming for patients and may lead to iron overload, potentially causing progressive damage to the liver, heart, and endocrine system. Many patients (80.9%) report experiencing fatigue, which may result in loss of independence, decreased physical activity, and functional decline, if severe or left untreated.[14,16,43]

DISCLOSURES

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Paroxysmal nocturnal hemoglobinuria: current treatments and unmet needs

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SUMMARY

The current standard of care for paroxysmal nocturnal hemoglobinuria (PNH) are the C5 inhibitors eculizumab and ravulizumab, both monoclonal antibodies designed to target the complement protein C5, thereby preventing its cleavage and the formation of the terminal attack complex. C5 inhibitors have yielded substantial improvements in the treatment of PNH and changed the mortality and morbidity, as well as health-related quality of life of patients with the disease. These treatments target underlying intravascular hemolysis; however, they do not address extravascular hemolysis, resulting in incomplete response and remaining symptoms in some patients. Therefore, despite treatment with a C5 inhibitor, some patients still experience anemia with associated fatigue, transfusion needs, and impaired health-related quality of life.

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